Chapter 1

Introduction

Emotional prosody

Emotional prosody is a paralinguistic aspect of language, consisting of features including intonation, stress, pitch, and volume. It is also known as the emotional melody of speech. When someone speaks to you, not only *what* someone says is important, but also *how* someone speaks. i.e. the tone of voice (Mitchell and Crow, 2005). The impact of saying to someone "You are a workaholic" has different meanings, depending on whether the tone of your voice is angry or playful. Emotional prosody gives information about the intention and emotional state of the speaker. Not being able to understand this information, and other social cues correctly, might lead to serious problems in social communication. This will be discussed in the paragraph on social cognition and schizophrenia.

A well established finding of neuroscience is that language is primarily lateralized to the left hemisphere. This means that in healthy (right-handed) people, the left hemisphere is dominant for language processing. Although such a role for the left hemisphere has been firmly established for processing of a range of linguistic aspects such as syntax and semantics, a number of lesion and imaging studies however, have revealed that the right hemisphere plays an important role in emotional prosody perception. The extent of the lateralization of emotional prosody to the right hemisphere differs between studies. Some researchers argue that it is solely the right hemisphere that pro-cesses emotional prosody (Ross et al., 1997;Ross, 1981;Ross and Monnot, 2008). Others have shown that bilateral brain regions are involved, with an asymmetry to the right hemisphere (Mitchell et al., 2003;Vingerhoets et al., 2003). Deficits in emotional prosody perception have also been found after left hemisphere lesions (Adolphs et al., 2002; Hornak et al., 2003). Studies examining the neural substrate of emotional prosody perception have revealed a network including bilateral regions in superior and middle temporal gyri and orbital and inferior frontal regions. Some studies have also implicated subcortical structures such as the amygdala (Sander et al., 2005;Phillips et al., 1998) and the basal ganglia (Pell and Leonard, 2003; Cancelliere and Kertesz, 1990). The results from studies examining the neural substrate of emotional prosody are as yet unclear with respect to which brain areas are involved in emotional prosody pro-cessing and with regard to the extent of lateralization of this function.

The aim of our studies in healthy subjects with the research technique transcranial magnetic stimulation (TMS) was to reveal whether certain areas that have been implied in emotional prosody processing would be critically involved in the process of emotional prosody perception and

more specifically at what time point during this process. Regions of interest for our first study (chapter 2) were based on imaging studies revealing an association with bilateral inferior frontal gyri (Ethofer et al., 2006;Buchanan et al., 2000). For the study described in chapter 3, the region of interest was based on a lesion study, concluding that the fronto-parietal operculum (FPO) is important for emotional prosody perception (Adolphs et al., 2002). Moreover, the FPO was also found to be involved in emotional prosody perception in a TMS study (van Rijn et al., 2005). Our study was a sequel and extension to this study of van Rijn et al. (2005).

Impairments in social cognition have been shown to be core deficits in schizophrenia (Couture et al., 2006). Among these, deficits in emotion processing, such as emotional prosody perception, are argued to be important for understanding the disorder (Aleman and Kahn, 2005).

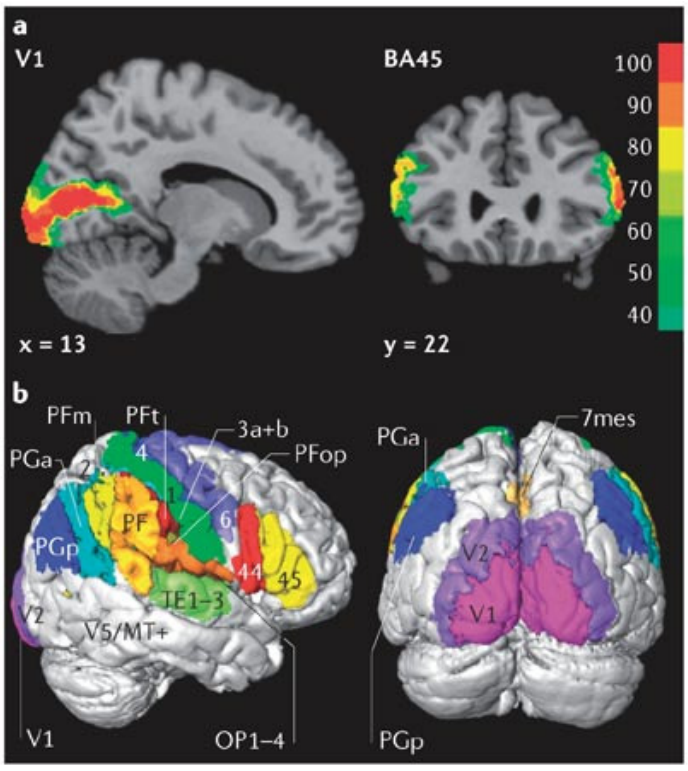

Figure 1 Cytoarchitectonic probability map of the cortex. Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Neuroscience* (Toga et al., 2006), copyright (2006). The inferior frontal gyrus (IFG), the region of interest in chapter 2 is Brodmann area (BA) 45 in the fi-gure, (46 is not shown this region is located a bit more frontal than BA 45). The region of inte-rest for the study described in chapter 3 is the fronto-parietal operculum, named PFop in the figure.

Schizophrenia

Kraepelin was the first who described what is now called schizophrenia (1899) (in (Jones and Buckley, 2006)). He used the term 'dementia praecox', for a syndrome of catatonia, hebephrenia and dementia paranoides. About ten years later Bleuler recognized the same syndrome also in youth and went on to use the term 'schizophreniagruppe', because he argued that splitting or tearing apart of the psychic functions that occurred in the syndrome formed the unifying feature and not the older age or deteriorating course (in (Cutting and Shepherd, 1987). He described in 1908 the disease as a decoupling of emotion, thoughts, and behaviour. The modern definition of schizophrenia includes many of the symptoms as observed and classified by Kraepelin and to a lesser extend by Bleuler. Its symptoms are defined in the in the internationally broadly used DSM classification of psychiatric diseases. Following the classification of schizophrenia according to the DSM-IV, it is in most cases a chronic disease. The symptoms of schizophrenia may affect many of the patient's thoughts, feelings, and behaviour. Its characteristics may include: abnormal perceptions in the form of hallucinations; aberrant inferential judgments that result in extraordinary beliefs and delusions; distorted thought construction that manifests as a disorder of language; unusual often restricted emotion, volition and hedonia; various cognitive problems mainly affecting memory and executive functions; seemingly strange behaviour understandable only in the context of these unusual experiences and abnormal control systems; finally, both motoric and developmental dimensions.

Symptoms like hallucinations and delusions are frequently classified as *positive symptoms*. Symptoms like lack of initiative and interest are often classified as *negative symptoms*. Not in the DSM-IV classification are the often observed *cognitive symptoms*, e.g. memory problems, and impairments in attention and problem solving. Impairments in a fourth domain, the *social cognition*, are the main subject of this thesis.

The group of patients fulfilling the DSM-IV criteria of schizophrenia is very heterogeneous (Jones and Buckley, 2006). Schizophrenia is mostly regarded as a neurocognitive disorder, with cognitive functions and the underlying neural system being most characteristic for the disease (Nuechterlein and Dawson, 1984; Heinrichs and Zakzanis, 1998). These are undeniably important characteristics; recently it has been proposed however, that aberrant social-emotional processing and its neural substrate may be even more important for understanding the disorder (Aleman and Kahn, 2005; Pinkham et al., 2003). Social-emotion processes forms part of social cognition, i.e.

all information processing underlying social interaction (see next paragraph) (Brothers, 1990). A growing body of evidence exists on impairments in social cognition in schizophrenia and more specifically on impairments in emotion processing. Disturbances in emotion can be divided in emotional expression, emotion perception, and experience of emotions. Schizophrenia patients show abnormalities in all three domains. The experience of emotion can however also be at normal (Kring and Earnst, 1999;Aghevli et al., 2003) or increased levels (Myin-Germeys et al., 2000). Abnormalities in neural systems involved in emotion processing have also been found. Different studies have revealed abnormal activation of the most important emotion related brain area, the amygdala, in during emotion processing in schizophrenia (Rasetti et al., 2009;Hall et al., 2008;Li et al., 2009). Most of these studies reported reduced activation of the amygdala to negative stimuli, which has been suggested to arise from an increased response to neutral stimuli (Hall et al., 2008). This is in line with the influential theory of aberrant salience, as will be described later (Kapur, 2003).

Schizophrenia is a syndrome usually having an onset in early adult life. Most patients develop symptoms between the ages of 16 and 26. The true beginning of the disease is often difficult to date. A collection of suspicious and disabling features may occur as a prodrome to schizophrenia. These prodromal features can be described as "not being themselves", "something is not quite right", and manifest as withdrawal from previous social roles, impairment in general functioning, behaviour others see as odd, altered emotions, deterioration in personal hygiene, difficulties communicating with others, strange ideas, unusual experiences and restricted drive (Jones and Buckley, 2006). A residual or stable phase follows the acute phases of illness and treatment. The features of this phase often resemble the prodromal phase with frequently some attenuated psychotic phenomena. However, emotional blunting or flattening of affect and impairments in social functioning are common.

Who gets schizophrenia?

The risk of developing schizophrenia over one's lifetime is just under 1 % (Tandon et al., 2008;Jones and Buckley, 2006). Environmental and genetic factors are involved in its causation. Urbanicity, male gender, migration, winter birth, obstetric and perinatal complications such as early childhood brain damage and well as cannabis or stimulant use in puberty are found to be associated with a higher risk to develop schizophrenia (Saha et al., 2006;Tandon et al., 2008). Having an affected family member substantially increases the risk of developing schizophrenia. First-degree relatives of people with schizophrenia (though this is a matter of debate) have a 3- 7% risk for

schizophrenia, this is 5-10 fold higher than for those with no schizophrenia in the family (Jones and Buckley, 2006). This risk increases as the degree of genetic affinity with the affected family member increases (Kendler et al., 1993). A meta-analysis on twin studies of schizophrenia, found an estimate of heritability of 81% (95% confidence interval, 73%-90%) (Sullivan et al., 2003). This means that twin studies have consistently found that among monozygotic twins the concordance for the disease is more than a three-fold greater than among dizygotic twins. However, the authors also determined that there are small significant common environmental effects on liability to schizophrenia (point estimate, 11%; 95% CI, 3%-19%) (Sullivan et al., 2003). Studies examining genetics in schizophrenia have pointed at several genes that possibly contributes to liability to the disease, one of these may be the COMT gene. Probably, liability for schizophrenia is built up in layers with multiple genes, including COMT, interacting with environmental factors such as prenatal risk factors, stress or drug use. At the level of the brain, schizophrenia may involve structural changes to different brain structures. The most consisting finding from neuroimaging studies on structural correlates of schizophrenia is enlarged cerebral ventricles, first found 30 yrs ago (Johnstone et al., 1976). But also changes to the prefrontal cortex, the corpus callosum (Wolkin and Rusinek, 2003) and to temporal regions (Lui et al., 2009) have been shown. Abnormalities in lateralization have been found in the temporal regions and in the ventricles, which may be related to the aetiology of psychosis (Sommer et al., 2001; Johnstone et al., 1989;Crow, 1990). It is thought that schizophrenia must involve many brain systems or sub-systems and, maybe even more important, their (functional) connections.

At present, there is no cure for schizophrenia; treatments are most effective when they are used in combination: cognitive behavioural therapy, psychotherapy, medication treatment, psychoeducation, family interventions, and social support. Various pharmacological therapies have been developed giving rise to different pharmacological models. The most influential of these models is the dopamine hypothesis, a model that focuses on imbalances in dopaminergic activity of the brain. According to this hypothesis, hyperactivity of the sub-cortical dopaminergic pathways mediates symptoms of psychosis, while hypo-activity of prefrontal dopaminergic pathways mediates negative and cognitive symptoms. The theory has been expanded, linking dopamine dysregulation to alterations in synaptic connectivity in the prefrontal cortex and that this alteration is related with N-methyl-D-aspartate (NMDA) hypofunction. Antipsychotic medication in use until 2009 target all the dopamine hyper-

activity, while some antipsychotics may also influence the glutaminergic (NMDA) system and other systems.

The dopamine hypothesis was a theoretical basis for the complementary hypothesis of 'aberrant salience' that aims to integrate findings from not only pharmacology but also biology and phenomenology in psychosis (Kapur, 2003). Dopamine is again the protagonist of this theory, especially its function in reward and reinforcement is thought to play a central role in the limbic system. The dopamine system has a mediating role in motivational salience. This means that the limbic dopamine system mediates the translation of the neural representation of an external stimulus from a neutral and unattractive bit of information into an attractive or aversive entity (Berridge and Robinson, 1998). Under normal circumstances, the limbic dopamine system is a mediator of contextually relevant saliences. In patients who experience psychosis the limbic dopamine system may become a creator of aberrant salience (Kapur, 2003). It has been proposed that before developing psychosis, patients develop an abundant release of dopamine, especially in the limbic system, independent of context or experiences. This leads to misattribution of salience and motivational significance to external and internal stimuli. In the earliest stages of a psychosis, this leads to the assignment of exaggerated importance to certain perceptions and ideas and may induce a perplexing state. This can also be described as a greater awareness, or a fascination for normally insignificant stimuli. Delusions can develop as a top-down cognitive explanation for these experiences of aberrant salience. The misattribution of salience to for other people neutral internal or external stimuli, e.g. neutral expressions in others, can also induce anxiety. According to this hypothesis, hallucinations arise from the abnormal salience of internal representations of perceptions and memories. This could explain the gradual differences in severity of hallucinations, whereby some people classify their hallucinations as their own internal thought, others as their own voice, and others as a third party. These events and experiences, together with other characteristics described in patients who are prone to psychosis related to schizophrenia, such as a tendency to jump to conclusions (Startup et al., 2008), deficits in attributional style and theory of mind (Lee, 2004;Penn et al., 2008) and abnormal levels of perceptual aberrations and ideation might interact with each other and lead to a more severe development of delusions and hallucinations (Kapur, 2003). The symptoms may deteriorate by the fact that patients with schizophrenia often show deficits in psychosocial functioning (Brekke et al., 2007) in cognition and in interpersonal relations. The interaction between the symptoms and deficits with the aberrant

neurochemistry determines different phenomenology of psychosis across individuals.

Another influential theory is the one proposed by Crow. The functional significance of hemispheric asymmetry has not been clarified yet. According to some theories the specialization of one hemisphere for a certain function has the advantage of no competition for processing between two identical messages, which implies a higher processing speed (Hugdahl, 2000). Simultaneous activation of homologue brain regions in both hemispheres is thought to blurr and slow down information processing (Hugdahl and Westerhausen, 2009). A variation of this theory is that specializing one hemisphere for a particular function leaves the other hemisphere free to perform other (additional) functions (Ringo et al., 1994;Levy, 1977). Hugdahl and Westerhausen have proposed that cerebral asymmetry may have evolved as a response to the evolutionary need for more effective interspecies communication, i.e. language (Hugdahl and Westerhausen, 2009).

Crow links abnormal lateralization of brain regions involved in language processing that has been found in schizophrenia, to the development of psychosis (Crow, 1990;Crow, 2000;2008). According to this hypothesis, a diminished cerebral asymmetry of language related brain areas is the key to the brain changes in schizophrenia. Crow argues that schizophrenia is the price homo sapiens pays for an evolutionary adaptation for language which requires left hemisphere specialisation (2000;Crow, 1990). From this concept developed the idea that language and psychosis are closely related, more specifically, it is thought that they have a common origin, probably located on the X-chromosome (Crow, 2000).

Anomalies in cerebral lateralization for language in schizophrenia have been widely reported. Not only for left hemisphere language functions (Sommer et al., 2001;Li et al., 2007;Artiges et al., 2000;Dollfus et al., 2005;Weiss et al., 2006;Weiss et al., 2004) but, interestingly some studies have also found abnormal lateralization for emotional prosody (Mitchell et al., 2004;Bach et al., 2009), a function that is normally lateralised to the right hemisphere (van Rijn et al., 2005;Adolphs et al., 2002).

Social cognition in schizophrenia

Most research focuses on negative or positive symptoms in schizophrenia. Impairments in social functioning are, however, a severe debilitating characteristic of the disease that merit further attention. Impairments in social functioning form one of the most devastating symptoms in schizophrenia. Not being able to develop and maintain a social network

and a stable work environment often leads to social isolation (Pinkham and Penn, 2006;Corrigan and Penn, 2001; Yager and Ehmann, 2006). According to Lee and colleagues, miscommunication is an important factor leading to deficits in social functioning (Lee, 2004). These miscommunications consist of misidentifying social information, like social rules, expressed emotions, and intentions of others. This can be partly due to a disability to understanding abstract expressions (Lee, 2004). It is thought that impairments in social cognition underlie social dysfunctioning (Couture et al., 2006). Social cognition can be defined as "the mental operations underlying social interactions, which include the human ability to perceive the intentions and dispositions of others" (Pinkham et al., 2003; Brothers, 1990).

Emotion perception forms part of social cognition and has been shown to be impaired in schizophrenia patients. Not only prosodic emotion perception but also facial emotion perception has been shown to be disturbed in schizophrenia (Edwards et al., 2002). This disturbed emotion perception can already be detected in the early stages of the development of schizophrenia (Edwards et al., 2001; Edwards et al., 2002;Mandal et al., 1998).

Studies have shown discrepant results with regard to the relationship between symptom dimensions and emotion perception. Positive symptoms (hallucinations and delusions) have been reported to correlate with impairments in facial emotion perception (Heimberg et al., 1992;Schneider et al., 1995) and vocal emotion perception (Shea et al., 2007). A relationship between more basic neurocognitive functioning and emotion perception from faces and voices has also been found (Bozikas et al., 2004; Tremeau, 2006;Schneider et al., 1995). There are mixed findings on the correlation between negative symptoms and emotion perception (Schneider et al., 1995;Mueser et al., 1996;Hofer et al., 2009). The relationships between impairments in perceiving emotional expressions and clinical variables merits further clarification. Another question that remains to be investigated is how these impairments might result in misattributions of emotions in others.

With our studies (chapter 5 and 6) we wanted to extend the knowledge about the relationship between emotion perception in others and symptom dimensions. In these studies, a five-factor model of the PANSS was used to measure symptom dimensions (van der Gaag et al., 2006). This model was the result of a ten-fold cross-validation over a large sample of in- and outpatients with schizophrenia (van der Gaag et al., 2006) generating five stable factors with little overlap reflecting: positive symptoms, negative symptoms, disorganization

symptoms, excitement and emotional distress (see table 1).

Table 1 PANSS five-factor model, Adapted from Van der Gaag et al. (2006)

PANSS items	Positive symptoms	Negative symptoms	Disorganization symptoms	Excitement	Emotional distress
P1 Delusions	**1.493 (.016)**				
P3 Hallucinations	**.964 (.021)**				
G9 Unusual thought content	**.975 (.021).**		**.407 (.020)**		
P6 Suspiciousness	**.846 (.020)**				***.354 (.020)***
P5 Grandiosity	**.522 (.023)**			**.321 (.026)**	
G1 Somatic concern	**.296 (.022)**				**.402 (.022)**
N6 Lack of spontaneity		**1.316 (.015)**			
N1 Blunted affect		**1.160 (.015)**			
N2 Emotional withdrawal		**1.106 (.015)**			
N4 Apathetic social withdrawal		**1.054 (.017)**			
G7 Motor retardation		**.784 (.017)**			
N3 Poor rapport		**1.188 (.016)**		**.232 (.016)**	
G16 Active social avoidance	**.105 (.020)**	**.690 (.020)**		**.166 (.022)**	**.223 (.020)**
N7 Stereotyped thinking			**.942 (.017)**		
G11 Poor attention			**.829 (.017)**		
G10 Disorientation			**.470 (.019)**		
P2 Conceptual disorganization		**-421 (.026)**	**1.380 (.023)**		
N5 Difficulty in abstraction	**-297 (.024)**		**1.109 (.022)**		
G5 Mannerism			**.672 (.018)**		
G12 Lack of judgment and insight	**.212 (.025)**		**.770 (.023)**		
G13 Disturbance of volition		**.291 (.026)**	**.622 (.025)**		
G15 Preoccupation			**.784 (.019)**		**.312 (.019)**
G14 Poor impulse control				**.921 (.018)**	
P4 Excitement				**.851 (.018)**	
P7 Hostility				**.797 (.019)**	
G8 Uncooperativeness		**.348 (.017)**		**.673 (.020)**	
G2 Anxiety					**1.215 (.018)**
G6 Depression					**.637 (.020)**
G3 Guilt					**.514 (.020)**
G4 Tension				**.262 (.020)**	**.724 (.019)**

Bold loadings were found in 10/10 analyses; italic loadings were found in 9/10 analysis; underlined loadings were found 6–8/10; normal loadings were found 3–5/10.

Magnetic Resonance Imaging

In the next paragraphs a short introduction to the techniques used in the experiments included in this thesis will be given. Magnetic Resonance Imaging (MRI) is a non-invasive way to study and visualize the structures of the living human brain. This method measures the concentration of water in different tissue types, based on the magnetic resonance of protons. A 3 Tesla MRI system (Philips Intera) has been used at the BCN NeuroImaging Center, in Groningen. For the experiments described in our studies, we made an anatomical scan for each subject. These scans result in high-resolution images with large contrasts between grey and white matter and cerebrospinal fluid. This allows the identification of separate brain regions and the determination of the subject's specific cerebral anatomy.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive, relatively painless, and reversible method for intervening with neural processing in the human brain. It is used to complement other neuroimaging techniques to map cortical brain functions or study central motor pathways and to evaluate cortico-cortical excitability (Toga and Mazziotta, 2002). TMS is also used as a treatment of psychiatric disorders, like Parkinson, tinnitus, depression, and auditory hallucinations.

Basic Mechanisms of TMS

The mechanism of TMS is based on Faraday's law of induction (1831). He discovered that a changing magnetic field creates an electric field. In TMS a very short, powerful current (a pulse) is generated and passed through a 'coil' of wire (Pascual-Leone et al., 2000; Pascual-Leone et al., 1993). This generates a transient magnetic field with a maximum strength of two Tesla (on the machine used in the experiments from this thesis). The researcher places the coil over the scalp of the participant. The changing magnetic field passes unimpeded and painlessly through the tissue of the head.

The coil is designed in an eight-shape such that it allows a focused magnetic field. The changing magnetic field creates a current in the participant's brain, thereby activating neurons at a depth of 1.5-2 cm. Importantly, a pulse may also indirectly affect neurons in remote brain regions that are functionally connected with the stimulated area.

The actual effect of TMS depends on: the intensity of stimulation (in % of the maximal output), the frequency of the pulses (in pulses per second (Hz)), the duration of stimulation, and the region of stimulation (Wassermann et al., 2008). Participants feel the pulses as a finger tap on their head. For some people however, the pulses are uncomfortable, depending on the place of stimulation, especially if

muscles may become stimulated. Stimulating certain frontal areas, e.g. the inferior frontal gyrus close to the temple, might lead to face and jaw muscle twitches.

There are different application forms of transcranial magnetic stimulation. The first and oldest is single pulse, 1 pulse is given over a single scalp position. With repetitive TMS (rTMS) a series of pulses is delivered in rapid succession, and the effect is summated over time. Slow rTMS or low frequency rTMS refers to a series of 1 Hz or less (which means 1 pulse per second or less). This has an inhibitory effect on the brain and thus reduces cortical excitability of the underlying cortex. Fast rTMS or high frequency rTMS refers to a series of 5 Hz or more. This has a facilitating effect on the brain and temporarily enhances the excitability of the cortex. It is not yet clear exactly how these changes are effectuated in the brain. It has been suggested that rTMS has effects akin to the physiological mechanisms of long term depression (LTD) and potentiation (LTP) of neurons (Wassermann et al., 2008). There are also indications that rTMS influences neurotransmitter systems, such as dopaminergic pathways (Wassermann et al., 2008) and GABA (Daskalakis et al., 2002). RTMS may produce longer lasting changes especially when administered in a repetitive way, in intervals over longer durations of time.

TMS as a research tool

The advantage of TMS above other imaging studies is that it allows the researchers to make causal inferences: TMS can be used as a virtual lesion technique by reducing excitability (low frequency rTMS) in a specified brain area temporarily (Walsh and Pascual-Leone, 2003). This can be analyzed by calculating changes in performance variables on the task. On the other hand, by stimulating excitability of a brain region (high frequency TMS), functions might be facilitated. By the use of fMRI, the brain areas associated with a function of interest can be studied, but whether this region is critical cannot be revealed without manipulating functions for instance with TMS. TMS does have limitations. Sometimes it is difficult to target the area of interest precisely. As mentioned before, the magnetic field not only affects underlying neurons, but also neighbouring ones and functionally connected ones. Furthermore, TMS can only reach gyri, but not sulci and no brain areas that are deeper than ± 2 cm in the brain. However, sulci and brain areas deeper in the brain may be targeted through TMS indirectly as these areas may have network connections with areas that can be reached with TMS.

Every TMS experiment starts with the determination of the individual motor threshold (MT). The MT is defined as the

lowest intensity that induces visible thumb movements in at least 5 out of 10 trials when TMS is applied over the motor cortex (Pridmore et al., 1998). In cognitive experiments, the subject is then seated in a comfortable chair in front of a computer. Precise coil placement is generally achieved by using a neural navigator system.

In fundamental TMS research, in which TMS can be used as a virtual lesion technique, two paradigms can be used: an *online* and an *offline design*. In the *online* design, TMS is applied during performance of the task. This design can also be used to analyze the time pattern of involvement of different brain areas in a certain function, then the pulse(s) is given at a given time point within a time-window of interest. In the *offline* design, tasks are performed after repetitive TMS is given for a number of minutes. Performance on the tasks is compared with performance in a baseline condition. The baseline condition can be either no TMS, placebo TMS or TMS over a control area, i.e. a brain region that has never been shown to be related with the function of interest. Which control condition is optimal, is still a matter of debate. In contrast to lesion studies, which typically measure behavioural deficits in terms of reduced accuracies, the virtual lesions induced by TMS generally manifest as changes in response times (RTs), rather than in percentages correct. TMS does not inactivate a region in the same way that a lesion does – instead it introduces random transient neural firing ('noise') into the process being performed. In most cases this leads to prolonged response times rather than actual errors (Wassermann et al., 2008). This is presumably because the information that remains unharmed in the neural network is sufficient to compensate for the noise, but this process requires extra time and manifests as prolonged response times. Consequently, increased reaction times after TMS can indicate that the targeted region is necessary for performing a task, even in the absence of errors.

Before each application of TMS, all participants have to complete a TMS checklist, to exclude all persons who have any of the potential risk factors such as metal in the head, epilepsy (in the family), or loss of consciousness in the past. Deliberations at the "International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (June 5–7, 1996)", made Wasserman (1998) propose guidelines for the safe use of TMS. These guidelines specify the three dimensional space defined by the variables of stimulus intensity, duration and frequency within which seizures are very unlikely to be observed. When consulting these guidelines and making use of the checklist for each participant, virtually all known risks are eliminated. Generally, TMS appears to be free from harmful effects (Wasser-

mann et al., 2008). Research using animals and human volunteers has shown little effect on the body in general as a result of stimulation, and examination of brain tissue submitted to thousands of TMS pulses has shown no detectable structural changes. Most common side-effect is a little headache, but this can be overcome by taking a paracetamol or will subside spontaneously.

Neuronavigation

To optimize the precise localization of the coil above a brain area of interest, neuronavigation systems have been developed. With help of these systems it is possible to select the area of interest based on individual anatomical or functional MR images. Functional MRI (fMRI) guided TMS is the most precise localization method for TMS.

For the TMS experiment described in chapter 2, the Neural Navigator (NeNa) was used to reliably localize the desired stimulation areas, of the participant (Neggers et al., 2004). The NeNa is a neuronavigation system developed by Neggers, based on magnetic fields (Neggers et al., 2004). A transmitter generates a pulsed magnetic field, which induces an electric current in the marker that is navigating to brain regions of interest. This current is then interpreted by an electronic unit to define locations in 3D space (Neggers et al., 2004).

For the TMS experiment described in chapter 3, we have used the BrainVoyager TMS Neuronavigator (BrainInnovation, Maastricht, The Netherlands). This frameless stereotaxic system allows for an online individual navigation of a TMS coil above a specific anatomical area of the brain, as well as a functional imaging-guided navigation of the TMS coil to functionally defined brain regions-of-interest. This in contrast to the NeNa that only allows offline navigation, meaning that during TMS no visualization can be given of correctness of placement and direction of the coil.

For the Brainvoyager TMS neuronavigor, Individual T1- weighed anatomical scans were analyzed in Brainvoyager QX 1.8 Software package such that a three-dimensional brain and a skin surface representation, were constructed and sulci and gyri were clearly visible and the specific region of interest could be drawn (BrainInnovation, Maastricht, The Netherlands). Anatomical landmarks were drawn on the skin surface reconstruction. For the co-registration of stereotaxic data and MRI data, an ultrasound system was used CMS30P (zebris, Tübingen, Germany). The local spatial coordinate system and the coordinate system of the MR space were co-registered. In this way, the system is able to "see" where the head of the participant is located in the 3-D space and where the coil is located relative the participant's head. After this

co-registration, the coil can be navigated precisely above the brain region of interest and all events (e.g. movements) occurring around the head of the participant in 3-D space are registered online and visualized in real-time at correct positions relative to the participant's anatomical reconstruction of the brain (Sack et al., 2006), see figure 2.

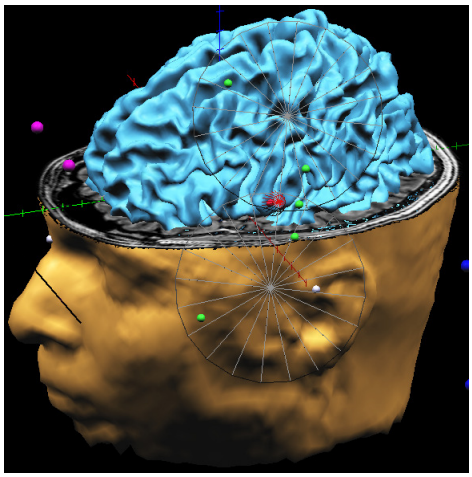

Figure 2 Online navigation of TMS coil towards brain region of interest, the fronto-parietal operculum.

Outline of this thesis

The studies described in this thesis are about emotion and language in healthy subjects and in people with schizophrenia. Language and emotion form the two corner stones of social communication, and for both, functional cerebral asymmetries have been found. With regard to language, the left hemisphere is dominant for most aspects, such as semantics, grammar and syntax. The right hemisphere however, has been shown to be important for paralinguistic aspects, such as emotional prosody, irony and metaphoric language (Mitchell and Crow, 2005;Mitchell et al., 2003;Pobric et al., 2008). Regarding emotion processing, theories assign different roles to the left and right hemisphere. The valence hypothesis states that hemispheric asymmetry for emotion processing depends on emotional valence (Hellige, 1993). The right hemisphere is dominant for negative emotions and the left hemisphere for positive emotions (Hellige, 1993). Another theory divides affect into two basic systems of approach and withdrawal (Davidson et al., 1990;Kinsbourne, 1978). Kinsbourne theorized that the left anterior region sub serves the approach system and the homologous right hemisphere region sub serves the withdrawal system (Kinsbourne, 1978). Interestingly, in schizophrenia, disturbances in both emotion and language have been reported and abnormalities in underlying cerebral lateralization have been found. The main part of the project described in this thesis is about emotional prosody, an aspect of language that bundles both language and emotion. To be able to study the possible aberrant lateralization of emotional prosody in schizophrenia, the neural substrate of this function first has to be clarified in healthy controls. This was the aim of **chapters 2 and 3**. The study described in **chapter 2** aims to help elucidating the neural underpinnings of emotional prosody by investigating the involvement of left and right inferior fron-

tal gyri in healthy subjects with the use of TMS. These brain areas have already shown to be associated in emotional prosody perception in fMRI studies, we wanted to study their critical involvement and a possible difference between left and right inferior frontal gyrus with regard to this function using TMS. In **chapter 3,** the temporal involvement of the right anterior superior temporal gyrus and the right fronto-parietal operculum in emotional prosody perception in healthy subjects is investigated using an online TMS design. Basis for this study is that the process of emotional prosody perception is proposed to be a multi-step process, each process being sub served by separate brain regions. The temporal regions are thought to be involved at an earlier stage than the frontal regions, which are thought to subserve the last steps. **Chapter 4** is a review and meta-analysis to evaluate the consistency and strength of the impairment in perception of emotional prosody in schizophrenia, using a quantitative review of published experimental studies. In this study, we wanted to review the literature on perception of emotional prosody in schizophrenia, to determine, by meta-analysis, the magnitude, and nature of impairments in perception of emotional prosody in schizophrenia, and to identify factors that significantly affect the magnitude of the impairment. **Chapter 5** aimed to extent the knowledge on the relation between clinical symptomatology and the recognition of emotion from language in a group of 83 schizophrenia patients. The ability to classify the emotions expressed in content or intonation of spoken language was correlated to five PANSS factors (Kapur, 2003). In **chapter 6** misattribution patterns in facial and vocal emotion perception in schizophrenia are studied in relationship with clinical symptomatology. In line with the aberrant salience theory, schizophrenia patients with psychotic symptoms often misattribute salience to stimuli that are experienced as neutral by others. In real world communication, this is expected to result in all kinds of miscommunications, because neutral expressions by others, may be interpreted as emotional by patients with a psychotic disorder. A summary of the studies and a discussion with clinical implications and future directions will be provided in **chapter 7**.

References

Adolphs,R., Damasio,H. and Tranel,D., 2002. Neural systems for recognition of emotional prosody: a 3-D lesion study. Emotion 2, 23-51.

Aghevli,M.A., Blanchard,J.J. and Horan, W.P., 2003. The expression and experience of emotion in schizophrenia: a study of social interactions. Psychiatry research 119, 261-270.

Aleman,A. and Kahn,R.S., 2005. Strange feelings: Do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Progress in neurobiology 77, 283-298.

Artiges,E. et al., 2000. Altered Hemispheric Functional Dominance During Word Generation in Negative Schizophrenia. Schizophrenia Bulletin 26, 709-721.

Bach,D.R. et al., 2009. Altered lateralisation of emotional prosody processing in schizophrenia. Schizophrenia research 110, 180-187.

Berridge,K.C. and Robinson,T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain research Brain research reviews 28, 309-369.

Bozikas,V.P., Kosmidis,M.H., Anezoulaki,D., Giannakou,M. and Karavatos,A., 2004. Relationship of affect recognition with psychopathology and cognitive performance in schizophrenia. Journal of the International Neuropsychological Society 10, 549-558.

Brekke,J., Hoe,M., Long,J. and Green,M., 2007. How Neurocognition and Social Cognition Influence Functional Change During Community-Based Psychosocial Rehabilitation for Individuals with Schizophrenia. Schizophrenia Bulletin sbl072.

Brothers,L., 1990. The Neural Basis of Primate Social Communication. Motivation and Emotion 14, 81-91.

Buchanan,T.W. et al., 2000. Recognition of emotional prosody and verbal components of spoken language: an fMRI study. Cognitive Brain Research 9, 227-238.

Cancelliere,A.E. and Kertesz,A., 1990. Lesion localization in acquired deficits of emotional expression and comprehension. Brain and cognition 13, 133-147.

Corrigan,P.W. and Penn,D.L., 2001. Social cognition and schizophrenia, 1st ed edn. American Psychological Association, Washington, D.C.

Couture,S.M., Penn,D.L. and Roberts,D.L., 2006. The Functional Significance of Social Cognition in Schizophrenia: A Review. Schizophrenia Bulletin 32, S44-S63.

Crow,T.J., 2000. Schizophrenia as the price that Homo sapiens pays for language: a resolution of the central paradox in the origin of the species. Brain research Brain research reviews 31, 118-129.

Crow,T.J., 2008. The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophrenia research 102, 31-52.

Crow,T.J., 1990. Temporal Lobe Asymmetries as the Key to the Etiology of Schizophrenia. Schizophrenia Bulletin 16, 433-443.

Cutting,J. and Shepherd,M., 1987. The Clinical roots of the schizophrenia concept
translations of seminal European contributions on schizophrenia Cambridge University Press, Cambridge.

Daskalakis,Z.J., Christensen,B.K., Fitzgerald,P.B. and Chen,R., 2002. Transcranial magnetic stimulation: A new investigational and treatment tool in psychiatry. Journal of Neuropsychiatry and Clinical Neurosciences 14, 406-415.

Davidson,R., Ekman,P., Saron,C. and Senulis,J., 1990. Approach^withdrawal and cerebral asymmetry: Emotional expression and brain physiology: I. Journal of Personality and Social Psychology 58, 330-341.

Dollfus,S. et al., 2005. Atypical hemispheric specialization for language in right-handed schizophrenia patients. Biological psychiatry 57, 1020-1028.

Edwards,J., Jackson,H.J. and Pattison,P.E., 2002. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. Clinical psychology review 22, 789-832.

Edwards,J., Pattison,P.E., Jackson,H.J. and Wales,R.J., 2001. Facial affect and affective prosody recognition in first-episode schizophrenia. Schizophrenia research 48, 235-253.

Ethofer,T. et al., 2006. Cerebral pathways in processing of affective prosody: A dynamic causal modeling study. NeuroImage 30, 580-587.

Hall,J. et al., 2008. Overactivation of fear systems to neutral faces in schizophrenia. Biological psychiatry 64, 70-73.

Heimberg,C., Gur,R.E., Erwin,R.J., Shtasel,D.L. and Gur,R.C., 1992. Facial emotion discrimination: III. Behavioral findings in schizophrenia. Psychiatry research 42, 253-265.

Heinrichs,R.W. and Zakzanis,K.K., 1998. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. Neuropsychology 12, 426-445.

Hellige,J.B., 1993. Hemispheric asymmetry - what's right and what's left Harvard University Press, Cambridge, Mass.

Hofer,A. et al., 2009. Facial emotion recognition and its relationship to symptomatic, subjective, and functional outcomes in outpatients with chronic schizophrenia. European Psychiatry 24, 27-32.

Hornak,J. et al., 2003. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain 126, 1691-1712.

Hugdahl,K., 2000. Lateralization of cognitive processes in the brain. Acta psychologica 105, 211-235.

Hugdahl,K. and Westerhausen,R., 2009. What Is Left Is Right How Speech Asymmetry Shaped the Brain. European Psychologist 14, 78-89.

Johnstone,E.C., Frith,C.D., Crow,T.J., Husband,J. and Kreel,L., 1976. Cerebral Ventricular Size and Cognitive Impairment in Chronic-Schizophrenia. Lancet 2, 924-926.

Johnstone,E.C. et al., 1989. Temporal-Lobe Structure As Determined by Nuclear Magnetic-Resonance in Schizophrenia and Bipolar Affective-Disorder. Journal of Neurology Neurosurgery and Psychiatry 52, 736-741.

Jones,P.B. and Buckley,P.F., 2006. Schizophrenia, 1 edn. Elsevier, Spain.

Kapur,S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. The American journal of psychiatry 160, 13-23.

Kendler,K.S. et al., 1993. The Roscommon Family Study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. Archives of general psychiatry 50, 527-540.

Kinsbourne,M., 1978. Asymmetry and the Brain. Science 200, 651-652.

Kring,A.M. and Earnst,K.S., 1999. Stability of emotional responding in schizophrenia. Behavior Therapy 30, 373-388.

Lee,K.H., 2004. Social cognition, brain networks and schizophrenia. Psychological medicine 34, 391-400.

Levy,J., 1977. The mammalian brain and the adaptive advantage of cerebral asymmetry. Annals of the New York Academy of Sciences 299, 264-272.

Li,H., Chan,R.C.K., McAlonan,G.M. and Gong,Q.y., 2009. Facial Emotion Processing in Schizophrenia: A Meta-analysis of Functional Neuroimaging Data. Schizophrenia Bulletin sbn190.

Li,X. et al., 2007. fMRI study of language activation in schizophrenia, schizoaffective disorder and in individuals genetically at high risk. Schizophrenia research 96, 14-24.

Lui,S. et al., 2009. Association of Cerebral Deficits With Clinical Symptoms in Antipsychotic-Naive First-Episode Schizophrenia: An Optimized Voxel-Based Morphometry and Resting State Functional Connectivity Study. American Journal of Psychiatry 166, 196-205.

Mandal,M.K., Pandey,R. and Prasad,A.B., 1998. Facial expressions of emotions and schizophrenia: A review. Schizophrenia Bulletin 24, 399-412.

Mitchell,R.L. and Crow,T.J., 2005. Right hemisphere language functions and schizophrenia: the forgotten hemisphere? Brain 128, 963-978.

Mitchell,R.L., Elliott,R., Barry,M., Cruttenden,A. and Woodruff,P.W., 2004. Neural response to emotional prosody in schizophrenia and in bipolar affective disorder. The British Journal of Psychiatry 184, 223-230.

Mitchell,R.L., Elliott,R., Barry,M., Cruttenden,A. and Woodruff,P.W., 2003. The neural response to emotional prosody, as revealed by functional magnetic resonance imaging. Neuropsychologia 41, 1410-1421.

Mueser,K.T. et al., 1996. Emotion recognition and social competence in chronic schizophrenia. Journal of Abnormal Psychology 105, 271-275.

Myin-Germeys,I., Delespaul,P.A.E.G. and deVries,M.W., 2000. Schizophrenia Patients Are More Emotionally Active Than Is Assumed Based on Their Behavior. Schizophrenia Bulletin 26, 847-854.

Neggers,S.F.W. et al., 2004. A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. NeuroImage 21, 1805-1817.

Nuechterlein,K.H. and Dawson,M.E., 1984. Information Processing and Attentional Functioning in the Developmental Course of Schizophrenic Disorders. Schizophrenia Bulletin 10, 160-203.

Pascual-Leone,A. et al., 1993. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalography and clinical neurophysiology 89, 120-130.

Pascual-Leone,A., Walsh,V. and Rothwell,J.C., 2000. Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. Current opinion in neurobiology 10, 232-237.

Pell,M.D. and Leonard,C.L., 2003. Processing emotional tone from speech in Parkinson's disease: a role for the basal ganglia. Cognitive, affective & behavioral neuroscience 3, 275-288.

Penn,D.L., Sanna,L.J. and Roberts,D.L., 2008. Social cognition in schizophrenia: an overview. Schizophrenia bulletin 34, 408-411.

Phillips,M.L. et al., 1998. Neural responses to facial and vocal expressions of fear and disgust. Proceedings of the Royal Society of London Series B 265, 1809-1817.

Pinkham,A. and Penn,D., 2006. Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. Psychiatry research 143, 167-178.

Pinkham,A.E., Penn,D.L., Perkins,D.O. and Lieberman,J., 2003. Implications for the neural basis of social cognition for the study of schizophrenia. The American journal of psychiatry 160, 815-824.

Pobric,G., Mashal,N., Faust,M. and Lavidor,M., 2008. The role of the right cerebral hemisphere in processing novel metaphoric expressions: A transcranial magnetic stimulation study. Journal of cognitive neuroscience 20, 170-181.

Pridmore,S., Fernandes,F.J.A., Nahas,Z., Liberatos,C. and George,M.S., 1998. Motor threshold in transcranial magnetic stimulation: A comparison of a neurophysiological method and a visualization of movement method. The journal of ECT 14, 25.

Rasetti,R. et al., 2009. Evidence That Altered Amygdala Activity in Schizophrenia Is Related to Clinical State and Not Genetic Risk. The American journal of psychiatry 166, 216-225.

Ringo,J.L., Doty,R.W., Demeter,S. and Simard,P.Y., 1994. Time Is of the Essence - A Conjecture That Hemispheric-Specialization Arises from Interhemispheric Conduction Delay. Cerebral cortex 4, 331-343.

Ross,E.D., 1981. The aprosodias. Functional-anatomic organization of the affective components of language in the right hemisphere. Archives of neurology 38, 561-569.

Ross,E.D. and Monnot,M., 2008. Neurology of affective prosody and its functional-anatomic organization in right hemisphere. Brain and language 104, 51-74.

Ross,E.D., Thompson,R.D. and Yenkosky, J., 1997. Lateralization of affective prosody in brain and the callosal integration of hemispheric language functions. Brain and language 56, 27-54.

Sack,A.T., Kohler,A., Linden,D.E., Goebel, R. and Muckli,L., 2006. The temporal characteristics of motion processing in hMT/V5+: Combining fMRI and neuronavigated TMS. NeuroImage 29, 1326-1335.

Saha,S., Welham,J., Chant,D. and McGrath,J., 2006. Incidence of schizophrenia does not vary with economic status of the country: evidence from a systematic review. Social psychiatry and psychiatric epidemiology 41, 338-340.

Sander,D. et al., 2005. Emotion and attention interactions in social cognition: Brain regions involved in processing anger prosody. NeuroImage 28, 848-858.

Schneider,F., Gur,R.C., Gur,R.E. and Shtasel,D.L., 1995. Emotional processing in schizophrenia: Neurobehavioral probes in relation to psychopathology. Schizophrenia research 17, 67-75.

Shea,T.L. et al., 2007. Emotional prosodic processing in auditory hallucinations. Schizophrenia research 90, 214-220.

Sommer,I.E.C., Ramsey,N.F. and Kahn, R.S., 2001. Language lateralization in schizophrenia, an fMRI study. Schizophrenia research 52, 57-67.

Startup,H., Freeman,D. and Garety,P.A., 2008. Jumping to conclusions and persecutory delusions. European Psychiatry 23, 457-459.

Sullivan,P.F., Kendler,K.S. and Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Archives of general psychiatry 60, 1187-1192.

Tandon,R., Keshavan,M.S. and Nasrallah,H.A., 2008. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophrenia research 102, 1-18.

Toga,A.W. and Mazziotta,J., 2002. Brain Mapping - The Methods, 2nd ed edn. Academic Press, Amsterdam.

Toga,A.W., Thompson,P.M., Mori,S., Amunts,K. and Zilles,K., 2006. Towards multimodal atlases of the human brain. Nature Reviews Neuroscience 7, 952-966.

Tremeau,F., 2006. A review of emotion deficits in schizophrenia. Dialogues in clinical neuroscience 8, 59-70.

van der Gaag,M. et al., 2006. The five-factor model of the Positive and Negative Syndrome Scale II: A ten-fold cross-validation of a revised model. Schizophrenia research 85, 280-287.

van Rijn,S. et al., 2005. What is said or how it is said makes a difference: role of the right fronto-parietal operculum in emotional prosody as revealed by repetitive TMS. European Journal of Neuroscience 21, 3195-3200.

Vingerhoets,G., Berckmoes,C. and Stroobant,N., 2003. Cerebral hemodynamics during discrimination of prosodic and semantic emotion in speech studied by transcranial Doppler ultrasonography. Neuropsychology 17, 93-99.

Walsh,V. and Pascual-Leone,A., 2003. Transcranial magnetic stimulation: a neurochronometrics of mind MIT Press, Cambridge, Mass.

Wassermann,E., Epstein,C.M. and Ziemann,U., 2008. Oxford handbook of transcranial stimulation Oxford University Press, Oxford.

Wassermann,E.M. Risk and Safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the safety of repetitive transcranial magnetic stimulation, June 5-7,1996. 1998.

Weiss,E. et al., 2006. Language lateralization in unmedicated patients during an acute episode of schizophrenia: A functional MRI study. Psychiatry Research: Neuroimaging 146, 185-190.

Weiss,E.M. et al., 2004. Brain activation patterns during a verbal fluency test--a functional MRI study in healthy volunteers and patients with schizophrenia. Schizophrenia research 70, 287-291.

Wolkin,A. and Rusinek,H., 2003. A neuropathology of psychosis? The Lancet 361, 270-271.

Yager,J.A. and Ehmann,T.S., 2006. Untangling social function and social cognition: a review of concepts and measurement. Psychiatry 69, 47-68.